

# Embryonic Testicular Regression Syndrome : A Case Report

MANEE RATTANACHAIYANONT, M.D.\*,  
KITIRAT TECHATRAISAK, M.D., Ph.D.\*,  
PHAIBUL JITPRAPHAI, M.D.\*\*\*

PHAKPHUM PHOPHONG, M.D.\*  
PICHAI CHAROENPANICH, M.D.\*\*

## Abstract

A case of testicular regression syndrome was reported. The patient was an 18 year old girl presenting with primary amenorrhoea. Physical examination revealed normal female external genitalia and underdeveloped secondary sexual characteristics. Hormonal profile indicated gonadal failure. Chromosome analysis revealed 46,XY karyotype. Diagnostic laparoscopy demonstrated undeveloped internal genital organs. Remnants of epididymis, vas deferens and seminiferous tubule were uncovered during exploratory laparotomy. Ontogeny of sexual differentiation and pathogenesis of testicular regression syndrome were reviewed and discussed.

**Key word :** Hermaphrodite, Testicular Regression

Embryonic testicular regression syndrome is a group of disorders characterized by 46,XY karyotype, abnormal sexual differentiation and lack of gonadal tissue at the time of birth<sup>(1)</sup>. It is not a common disorder. The case presented here is the second case in Siriraj Hospital, whereas, the first case was reported more than 10 years ago<sup>(2)</sup>.

Previous investigators have suggested that this condition results from disappearance of testes at a critical stage in development<sup>(3)</sup>. In consequence,

the disappearance of testes affects the development of external and internal genital organs. The clinical features depend on the gestational age when testes disappear<sup>(4-6)</sup>. They may be (1) female with normal external and internal genital organs like pure gonadal dysgenesis except that no dysgenetic gonads are found, (2) female with ambiguous genitalia but without internal genital organs, (3) male with micropenis, normal sexual ducts but without testes or (4) male with normal genitalia and sexual ducts but without testes.

\* [Division of Reproductive Endocrinology]

\*\* Division of Pathology, Department of Obstetrics and Gynaecology,

\*\*\* Division of Urosurgery, Department of Surgery, [Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.]

It is believed that the causes of testicular disappearance might be vascular accident<sup>(7)</sup> or causative agents such as some viral infection that occurred during the critical stage. In addition, there is evidence that this disorder is part of the clinical spectrum of 46,XY gonadal dysgenesis and that genetic basis plays a role in this condition<sup>(3)</sup>. In other words, it is not simply disappearance of normal testes or of the testis-to-be gonads. Thus, the clinical features can vary and may not fit typically with those 4 features mentioned in the previous paragraph.

Our case supports the evidence that this condition is not simply a disappearance of testes.

### CASE REPORT

An 18-year-old girl, V.A. (HN 176261-34), presented with primary amenorrhoea. She did not develop secondary sexual characteristics. She had no episodes of undue stress, strenuous exercise or weight change. She had normal eye sight, no chronic headache, and no history of head injury. She did not have cyclic abdominal pain. Her past medical history was uneventful. There were no apparent genetic or communicable diseases in the family. She was the sole daughter in her family. All of her 6 brothers were in good health. To her mother's knowledge, she and her husband were not relatives.

Physical examination revealed a healthy young woman with normal intelligence. The vital signs were normal. Her general appearance did not have any stigmata suggesting any syndrome. Her height was 154 cm; span was 156 cm; weight was 47.7 kg. There were no hirsutism or thyromegaly. Cardiopulmonary and abdominal examinations were within normal limit. External genitalia revealed poorly developed secondary sexual characteristics; breasts were in Tanner stage B2 and pubic hair was in Tanner stage P2. No abnormal mass was palpated at the inguinal region or genital area.

Pelvic examination revealed normal female infantile genitalia, intact hymenal ring and 2-inch-depth vaginal canal. No uterus was palpable on both pelvic and rectal examination.

Laboratory investigation revealed a hypo-estrogenic stage maturation index on pap smear from vaginal mucosa. Karyotype was 46,XY using peripheral lymphocytes culture with G-banding. The Y chromosome in all 30 metaphase lymphocytes appeared to be morphologically normal.

Hormonal study using radioimmunoassay reported FSH 64 mIU/ml, LH 21 mIU/ml TSH 0.5 uIU/ml and Prolactin 12 ng/ml.

Transabdominal pelvic ultrasonography demonstrated no gonads or uterus in the pelvic cavity.

Chest X-ray was in normal limits. No abnormality in the urinary system was demonstrated in the intravenous pyelogram. Bony structures showed no abnormality in the radiological examination.

Diagnostic laparoscopy revealed undeveloped internal genital organs. No definite gonad could be seen either in normal or abnormal location. Since the patient had Y chromosome and no gonad could be demonstrated *via* these means, exploratory laparotomy was considered.

During operation, a small tubular-like structure, measuring 0.5x0.5x2 cm was palpated at the posterior wall of the bladder which was dissected. Both inguinal canal were explored: no evidence of gonadal tissue was found. The retroperitoneal space was explored up to the lower pole of both kidneys: no gonadal tissue was found.

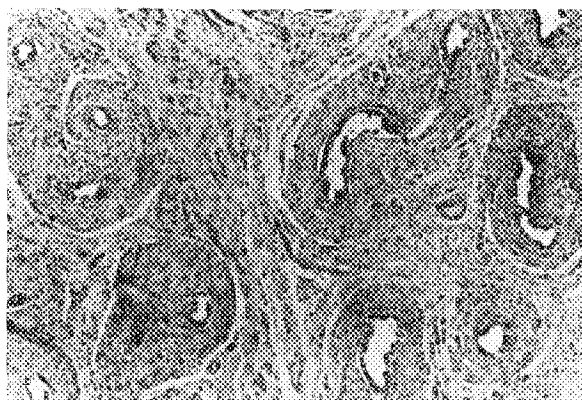
Histopathology of step sections of the tubular structures showed a muscular tubular structure in one slide, multiple smaller muscular tubular structures lying in groups suggesting tortuosity of the structure in the other slide. They were compatible with vas deferens and epididymis respectively (Fig. 1). Interestingly, there was a section which showed a group of tiny thin wall tubular structures lined with clear columnar cells that were consistent with Sertoli cells. The structure was compatible with seminiferous tubules (Fig. 2).

After operation, the patient received 0.625 mg conjugated equine estrogen daily as a replacement therapy. She has been followed-up every 6 months for 6 years since her operation. Her secondary sexual characteristics developed to stage B4 and P3. No gonadal tumor has developed yet.

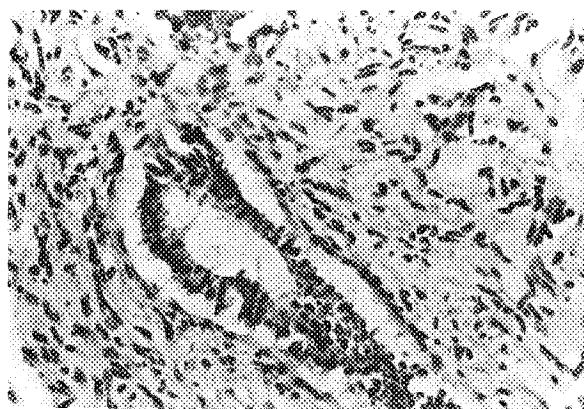
### DISCUSSION

In sexual differentiation, genetic sex begins at the conception but the differentiation does not occur until approximately 7 or 8 weeks of gestational age in the embryo with or without Y chromosome respectively<sup>(4)</sup>.

In the presence of the Y chromosome, the testicular determining factor (TDF) is produced



**Fig. 1.** Histopathology of the patient shows epididymis.



**Fig. 2.** Histopathology of the patient shows Sertoli cells in seminiferous tubule.

from TDF gene, which is later known to be sex determining region Y (SRY) gene<sup>(8)</sup>. Apart from the Y chromosome (or more exactly SRY gene), there are other genes on autosome that are demonstrated to have testicular determination<sup>(9)</sup>. Consequently, bipotential gonads develop to be testes. The developing testes secrete two hormones, mullerian inhibiting substance (MIS) from Sertoli cells and testosterone (T) from Leydig cells. MIS inhibits the proliferation of mullerian ducts thus, the development of a uterus, fallopian tubes and the upper part of the vagina are impossible. This process begins at 7-8 weeks and are complete by early second trimester<sup>(3,4)</sup>. T induces the proliferation of wolffian ducts which will develop to be epididymis, vas deferens

and seminal vesicle. Enzyme 5- $\alpha$  reductase in peripheral tissues converts T to dihydrotestosterone (DHT) which promotes masculinization of the external genitalia. These latter two processes begin at 10 weeks and are complete by 16-17 weeks of gestation<sup>(10)</sup>.

In the absence of the Y chromosome, the bipotential gonads automatically develop to ovaries with an exception in the embryo with an abnormal X chromosome that the gonads may be dysgenesis. Without MIS, the mullerian ducts develop to a uterus, fallopian tubes and upper part of the vagina. Without T, Wolffian ducts are degenerated. Without DHT, external genitalia automatically develops to be female genitalia.

The sexual differentiation of embryos does not always follow the rule. There have been occasional reported cases of sex reversal XY female and XX male. The pathogenesis in some but not all cases of XX male could be explained that the SRY gene--the gene that should be present normally on the short arm of the Y chromosome--was present in such cases. The pathogenesis in the more common XY female cases could vary on any step of male sexual development, i.e. agenesis of gonads (gonadism), nonfunctioning dysgenetic gonads (gonadal dysgenesis), disappearance of gonads or testes during late embryo or early fetal life (embryonic testicular regression), absence of normal androgen receptor (androgen insensitivity or testicular feminization), or absence of 5- $\alpha$  reductase enzyme.

In this case, there is evidence that the testes did exist during the developmental period. The residual seminiferous tubule--a Sertoli cell lining tubular structure as shown in the pathological sections--confirmed the existence of testicular tissue but it had no function in her adolescent age since there was no spermatogenesis in the tubule, not enough androgen secretion for virilization and not enough inhibin for suppression of gonadotropins. The absence of mullerian derived structures suggest that the Sertoli cells must normally function secreting MIS to at least 14 weeks of gestation<sup>(3)</sup>. The residuals of epididymis and vas deferens suggest that at least one testis must function secreting T for some time between 10 and 18 weeks of gestation before regression<sup>(3)</sup>. From the above evidence, the patient must have had a functioning testis to at least 14 weeks of gestation. By that time, her external genitalia should have developed to the ambiguous type or even male pattern, but ironically, she had

normal female genitalia. Her normal genitalia suggest that the testis might have abnormal function secreting androgen inadequate for masculinization of genitalia or she might have 5- $\alpha$  reductase deficiency as an associated defect. With a deficit in this enzyme, the patient could not produce DHT for masculinization of the genitalia.

Marcantonio SM et al (1994) introduced a concept that testicular regression sequence is part of the clinical manifestation of 46,XY gonadal dysgenesis and the cause of this syndrome is related to mutation in one of the gene(s) that are critical for the early stage of testis determination or differentiation after the action of TDF. The manifestation in this patient supports this concept in that the testis is abnormal prior to its regression but with the labora-

tory facilities in our institute, we could not prove whether the patient had a defective SRY gene, 5- $\alpha$  reductase gene or other genes concerning testis determination.

In the case of impalpable gonads, laparoscopy will be beneficial both for diagnosis and further management(11-13). In this case, the diagnosis was done by diagnostic laparoscopy. Further management is controversial. Is exploratory laparotomy necessary? There are many reports that when the preoperative laparoscopy revealed absence of gonads, exploration will be neglected(14,15). In spite of a negative laparoscopic finding, the suspected gonadal tissue was found in this case. Hence, the patient pertained risk of a gonadal tumor if the gonadal tissue was not removed.

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## REFERENCES

- Overzier C, Linden H. Echter Agnathismus (Anorchismus) bei Geschwistern. *Gynaecologia* 1956; 142:215-20.
- Unakul W, Anuman-Rajadon Y. The XY gonadal agenesis : A case report. *J Med Assoc Thai* 1986; 70:475-7.
- Marcantonio SM, Fechner PY, Migeon CJ, Perlman EJ, Berkovitz GD. Embryonic testicular regression sequence: A part of the clinical spectrum of 46, XY gonadal dysgenesis. *Am J Med Genet* 1994;49: 1-5.
- Speroff L, Glass RH, Kase NG. Normal and abnormal sexual development. In: Speroff L, Glass RH, Kase NG, eds. *Clinical Gynecologic Endocrinology and Infertility*. 5th.ed. Williams&Wilkins : Baltimore, 1994:321-60.
- Coulam CB. Testicular regression syndrome. *Obstet Gynecol* 1979;53:44-9.
- Josso N, Briard ML. Embryonic testicular regression syndrome: variable phenotypic expression in sibling. *J Pediatr* 1980;97:200-4.
- Smith NM, Byard RW, Bourne AJ. Testicular regression syndrome a pathological study of 77 cases. *Histopathology* 1981;19:267-72.
- Sinclair AH, Berta P, Palmer MS, et al. A gene from human sex-determining region encodes a protein with homology to a conserved DNA-binding motif. *Nature* 1990;346:240-4.
- Tommurup N, Schempp W, Meimeche P, et al. Assignment of autosomal sex reversal locus (SR A1) and campomelic dysplasia (CMPD1) to 17q24.3-q25.1. *Nature Genet* 1993;4:170-4.
- Jirasek JE. Development of the genital system and male pseudohermaphroditism. The Johns Hopkins Press : Baltimore, 1971.
- YUTJ, Shu K, Kung FT, Eng HL, Chen HY. Use of laparoscopy in intersex patients. *J Urology* 1995; 154:1193-6.
- Kristiansen SB, Doody KJ. Laparoscopic removal of 46,XY gonads located within the inguinal canals. *Fertil Steril* 1992;58:1076-7.
- Wilson EE, Vuitch F, Carr BR. Laparoscopic removal of dysgenetic gonads containing a gonadoblastoma in a patient with Swyer syndrome. *Obstet Gynecol* 1992;79:842-4.
- Poltzker ED, Rushton HG, Belman AB, Skoog SJ. Laparoscopy for nonpalpable testis in childhood: Is inguinal exploration also necessary when vas and vessels exit the inguinal ring? *J Urol* 1992; 148:635-7.
- Tennenbaum SY, Lerner SE, McAleer IM, Packer MG, Sxherz HC, Kaplan GW. Preoperative laparoscope localization of the non palpable testis: a critical analysis of a 10-year experience. *J Urol* 1994;151:732-4.

## กระเทยเทียมจากการเสื่อมสลายของอวัยวะในกระเพาะปัสสาวะ : รายงานผู้ป่วย 1 ราย

มณี รัตนไชยานนท์, พ.บ.\*, ภาคภูมิ โพธิ์พงษ์, พ.บ.\*,  
กิติรัตน์ เดชะไตรศักดิ์, พ.บ., Ph.D.\*, พิชัย เจริญพานิช, พ.บ., \*\*,  
ไพบุลย์ จิตประไพ, พ.บ.\*\*\*

รายงานผู้ป่วย 1 ราย อายุ 18 ปี มีภาวะขาดระดับรูมูมิ การตรวจร่างกายพบรูปร่างภายนอกเป็นหญิง แต่ไม่มีการเจริญของลักษณะทางเพศเมื่อเข้าสู่วัยสาว ผลการตรวจฮอโมนเพศแสดงถึงภาวะต่อมเพศไม่ทำงาน ผู้ป่วยมีโครโมโซม 46,XY ตรวจไม่พบมดลูกและอวัยวะสืบพันธุ์ภายในช่องท้อง แต่พบมีส่วนหลงเหลือของลูกอัณฑะ และท่อนำเชื้ออสุจิ ภาวะกระเทยเทียมชนิดนี้เกิดจากการเสื่อมสลายของอวัยวะเพศชายที่ผู้ป่วยเป็นกระเพาะปัสสาวะในครรภ์มารดา ผู้รายงานได้วิจารณ์พยาธิกำเนิดและศัพทวิทยาของภาวะนี้

**คำสำคัญ :** กระเทยเทียม, การเสื่อมสลายของอวัยวะ

- \* สาขาวิชาต่อมไร้ท่อและเมตาบอลิซึม,
- \*\* สาขาวิชาพยาธิวิทยา, ภาควิชาจุลชีววิทยาและปรสิตวิทยา,
- \*\*\* สาขาวิชาศัลยศาสตร์ระบบทางเดินปัสสาวะ, ภาควิชาศัลยศาสตร์, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพฯ ๙ 10700